DETAILED ACTION

A preliminary amendment was received 12/30/2005, cancelling claims 1, 7-12, 15, 17-19, 21-26, 33-38, 41-45, 47-52, 56 and 58; no claims were amended; no claims were added. Claims 2-6, 13, 14, 16, 20, 28-32, 39, 40, 46, and 53-57 remain pending in the current application, all of which have been considered on the merits.

Priority

The instant application is a national stage filing under 35 USC 371 of PCT/US04/21414, filed 7/1/2004. Acknowledgement is made of Applicants' claims for priority under 35 USC 119(e) to U.S. provisional applications 60/484,563, filed 7/1/2003, and 60/484,595, filed 7/2/2003.

Oath/Declaration

The oath or declaration is defective because it does not provide a post office address for inventor Robert T. Tranquillo, only the city of residence is provided. A mailing address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing address should include the ZIP Code designation.

The mailing address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

Claim Objections

Claims 2, 28, 55 and 57 are objected to for minor informalities:

Claim 2 contains the first instances of the abbreviations **ECs** and **SMCs** without reciting the full term in accompaniment. The first time an abbreviation is used in the claims it should be preceded by the

full term, for example: Claim 2, lines 4-5 "…said matrix having incorporated therein at least endothelial cells (ECs) and smooth muscle cells (SMCs), said matrix...."

Furthermore, claim 2 does not end with a period, correction is required.

In claim 2 line 3, claim 28 line 4, claim 55 line 2, and claim 57 line 6, it appears "mitogenic" should be followed by the word "factors". Correction is required.

In claim 57 the index terms **a. b.** and **c.** should be replaced with **a) b)** and **c)** because periods should not technically be used in claims except for at the end of the sentence and in abbreviations. See *Fressola v. Manbeck,* 36 USPQ2d 1211 (D.D.C. 1995). MPEP 608.1(m). Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-6, 13, 14, 16, 20, 27 and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The method of claim 2 is considered indefinite because the language is not so clear as to define what steps are intended as part of the claimed method.

Claim 2 recites a method of making an engineered blood vessel comprising an endothelial intimal layer surrounded by a smooth muscle medial layer, said method comprising:

contacting one or more mitogenic [factors] with one or more attractant factors or one or more mitoattractant factors or combinations thereof with a matrix ;

said matrix having incorporated therein at least ECs and SMCs,

said matrix and cells being circumferentially positioned around a tubular support,

said factors having been added to the inside of the tubular support,

said support having allowed said factors to move from the inside of the tube to the ECs in the matrix,

wherein said contacting results in the formation of said endothelial intimal layer surrounded by said smooth muscle medial layer.

In the single step of "contacting one or more mitogenic [factors] with one or more attractant factors or one or more mitoattractant factors or combinations thereof with a matrix" it is unclear what exactly is being contacted with what. It appears the one or more mitogenic [factors] is contacted with one or more attractant factors, one or more mitoattractant factors, or combinations thereof; it is not clear how the matrix is involved, if at all. In abstract terms the claim reads "contacting A *with* B, C or D *with* E". The grammar renders it unclear if "D with E" is a single species ("A *with* B, C or D/E"), if "E" is another alternative to "B", "C" and "D" ("A *with* B, C, D, or E"), or if "E" is required in addition ("A *with* B, C or D, *and further with* E"). Clarification is required.

Furthermore, it is not clear if the recitations "said factors having been added to the inside of the tubular support" (Claim 2, line 5-6), and "said support having allowed said factors to move from the inside of the tube to the ECs in the matrix" (claim 2, lines 6-7) are intended to be active steps that are carried out as part of the method, of it they are steps that were carried out prior and are not required? Still further, it is confusing because the claim does recite a step of contacting the factors with one another and/or the matrix, thus it is unclear how (or why) the factors are added to the inside of the tubular support? It is noted that the support 'ha[s] allowed factors to move from the inside of the tube to the ECs in the matrix', but this would infer that the factors are not placed in contact with the matrix in the first step. Clarification is required.

In claim 20 it is not clear what the limitation "the factor" is referring to, as several factors are recited in claim 2; it is not clear which 'factor' is limited to vascular endothelial growth factor.

In claim 46 it is not clear what the limitation "the factor" is referring to, as several factors are recited in claim 28; it is not clear which 'factor' is limited to vascular endothelial growth factor.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2-6, 13, 14, 16, 27-32, 39, 40, 53-55 and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Niklason et al (Science, 1999), in light of Henrikson (Ed.) Histology (1997).

Niklason et al disclose methods for producing tissue engineered blood vessels (TEBVs) comprising an endothelial intimal layer surrounded by a smooth muscle medial layer, and the TEBVs thereby produced. Both the methods of making the TEBVs and the TEBVs, per se, are considered to read on the claims of the instant invention.

Specifically, Niklason et al disclose providing tubular, biodegradable mesh scaffolds of polyglycolic acid (PGA) (which reads on a tubular support which permits migration of factors through the material); culturing smooth muscle cells (SMCs) on the scaffolds to form a natural matrix on the exterior surfaces of the scaffold; seeding endothelial cells (ECs) on the matrix formed by the SMCs on the luminal surface of the scaffold (which reads on a matrix, having incorporated therein ECs and SMCs, the matrix and cells being circumferentially positioned around the tubular support); and culturing the vessel by pulsating culture media through the lumen of the vessel, thereby forming a TEBV with a defined

endothelial intimal layer surrounded by a smooth muscle medial layer (See Niklason et al, Pg. 490, col. 2-3 & Fig. 1). The culture media contained DMEM supplemented with 20% fetal bovine serum, penicillin, Hepes, ascorbic acid, copper sulfate, proline, alanine and glycine, because this media supported EC growth, each component is considered to read on mitogenic, attractant, and mitoattractant factors, and thus culturing the TEBV reads on contacting the matrix with one or more mitogenic, attractant and/or mitoattractant factors to form a mature endothelial intimal layer surrounded by a mature smooth muscle medial layer. The culture media may be considered a pharmaceutically acceptable carrier; the TEBV in the culture media therefore reads on a pharmaceutical composition (claims 2, 16, 27, 28, 53-55 and 57)

Smooth muscle cells naturally secrete type IV collagen (See Henrikson et al, Histology, page 98); thus the matrix produced by the SMCs inherently comprises collagen (claim 14 and 40).

The source of the cells, as recited by claims 3-6, 13, 29-32 and 39, are submitted to be product-by-process limitations. Product-by-process limitations are considered only insofar as the method of production (or in the instant case, the original source of the cells) imparts distinct structural characteristics or properties to the product being claimed (in the instant case, the ECs and SMCs used in the blood vessel). However, if the product, as claimed, is the same or obvious over a product of the prior art (*i.e.* is not structurally distinct), the claim is considered unpatentable over the prior art, even though the prior art product is made by a different process. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985), and *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979). In the instant case, requiring the ECs and SMCs to be *derived* from stem cells does not impart any structural distinction to the adult ECs or SMCs; in fact, it is submitted all cells are ultimately *derived* from stem cells. Therefore, the source of the cells does not differentiate over the teachings of Niklason et al, and claims 3-6, 13, 29-32 and 39 are properly included in the rejection of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 13, 14, 16, 20, 28-32, 39, 40 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niklason et al (Science, 1999), in light of Henrikson (Ed.), Histology (1997), and in view of Tu et al (US Patent 6,506,398).

The teachings of Niklason et al and Henrikson et al are set forth above. Niklason et al disclose a method of producing tissue engineered blood vessels (TEBVs) and TEBVs thereby produced that anticipate the methods and compositions of claims 1-6, 13, 14, 16, 28-32, 39 and 40.

Niklason et al differs from the current invention in that they do not disclose inclusion of vascular endothelial growth factor (VEGF) in the culture media. However, it is submitted that inclusion of VEGF in culture media for a tissue engineered blood vessel construct comprising endothelial cells would have been *prima facie* obvious to one of ordinary skill in the art because use of VEGF with tissue engineered blood vessels was well known in the art, see Tu et al.

Tu et al clearly disclose VEGF to be a mitogenic factor for vascular endothelial cells, and suggests inclusion of VEGF in vascular grafts to enhance vascular endothelial cell recruitment and proliferation (See Tu et al, abstract & col. 4, ln 1-11). Therefore the artisan of ordinary skill would have been motivated to include VEGF in the culture media utilized by Niklason et al in order to improve the EC patency within the graft. One would have had a reasonable expectation of successfully utilizing VEGF based on the express teachings of Tu et al. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON M. FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 8:00-6 M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Examiner, Art Unit 1651